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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/328,975	06/09/1999	JOHN A. WOLFF	MIRUS009	7574

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MIRUS CORPORATION
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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/328,975	WOLFF ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8* is/are allowed.

6)☒ Claim(s) *1,3,5 and 7* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 1999* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 1/27/06.

Claims 1, 3, 5, and 6-8 remain pending and are under consideration in this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5, and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Degols et al (Nucl. Acids Res. 19(4): 945-948, 1991) in view of Leonetti et al (J. Nat. Cancer Inst. 88(7): 419-429, 1996), taken with the evidence of Wiethoff et al (J. Biol. Chem. 276(35): 32806-32813, 2001).

Degols taught methods of inhibiting the proliferation of tumor cell in vivo by forming a composition comprising an anti-*c-myc* anti-sense oligonucleotide conjugated to polylysine, and then forming a ternary complex by addition of polyanions such as heparin, carboxymethylcellulose, alginate, and polyglutamate. See abstract; page 946, column 1, first full paragraph, and Fig. 2 at column 2; page 947 column 1, second full paragraph, and Fig. 3; page 947, column 2, second full paragraph. Degols was silent as to the net charge of the ternary complexes.

Evidence that the ternary complexes had a net negative charge is as follows. To form ternary complexes, Degols used polyanions at a concentration of 100 micrograms/ml, and polylysine(PLL)/oligonucleotide conjugates in a range of concentrations from 1-2 micromolar. Each oligonucleotide was modified with a PLL molecule at the 3' ribose, so each conjugate contained one molecule of PLL, molecular weight 14000. See page 945, column 2, last full paragraph through page 946, column 1, line 6. Assuming a residue molecular weight of 128.2 Da for lysine, 14 kDA PLL has a net charge of 109 positive charges per mole at physiological pH. The myc oligonucleotides were 17 nucleotides in length, so assuming 1 negative charge per nucleotide, the net charge of each conjugate was about 109-17 = 92 positive charges. So, if Degols used the conjugates at 1-2 micromolar, this is equivalent to a concentration of positive charges of about 92-184 micromolar.

Wiethoff taught that heparin contains an average of 2.4 sulfates and 1 carboxylate per repeating disaccharide, and that each disaccharide has a molecular weight of 535 Da. See page 32807, column 1, lines 3-8 of the fourth full paragraph. So, if heparin has 3.4 moles of negative charge per every 535 g, then it contains 0.64 micromoles of negative charge per 100 micrograms. To form ternary complexes, Degols used heparin at concentration of 100 micrograms/ml, i.e. 0.64 micromoles/ml, or 640 micromolar. Thus, in forming ternary complexes, Degols added negative charges to positive charges at a ratio of 640 micromoles to 92-184 micromoles. Absent evidence to the contrary, this led to the formation of negatively charged ternary complexes.

Degols did not teach a method of delivering the complexes in vivo.

Leonetti taught a method of delivering anti-*c-myc* anti-sense oligonucleotides to melanoma cells in mice. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the ternary complexes of Degols in the method of Leonetti. One would have been motivated to do so because Degols showed that use of the ternary complexes allowed one to achieve the same anti-proliferative effect with one tenth the amount of oligonucleotide. Compare Figs. 1 and 2 on page 946. Also Degols taught that polyanions inhibit the normal fusion of secondary lysosomes with phagosomes, leading to decreased degradation of endocytosed molecules. See page 948, lines 7-11 of the paragraph bridging columns 1 and 2.

Thus the invention as a whole was prima facie obvious.

The following rejection is made against an embodiment of the claims as newly amended in which there is no covalent linkage between the polycation and the nucleic acid.

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem. 269(29): 14621-14624, 1988) in view of Degols et al Nucl. Acids Res. 19(4): 945-948, 1991).

Wu taught formation of ionic complexes of polylysine and DNA and a method of delivering the complexes to cells in vivo. See abstract.

Wu did not teach formation of a complex having a net negative charge by ionically associating a polyanion with the polylysine/DNA complexes.

The teachings of Degols are discussed above. Degols taught that the toxicity of polylysine in delivery complexes can be reduced by formation of a ternary complex with an excess of polyanions such as heparin, carboxymethylcellulose, alginate, or polyglutamate. See abstract, page 945, column 2, last sentence of first full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add a polyanion to the complex of Wu to form a negatively charged ternary complex prior to administration. One would have been motivated to do so to decrease the toxicity of the polylysine as taught by Degols. One could also reasonably expect addition of the polyanions to increase the stability of the complexes against nucleases, as well as to inhibit the maturation of endosomes to lysosomes after uptake of the DNA, thereby facilitating escape of the DNA from endosomes into the cytoplasm. See Degols at page 948, column 1, lines 1-3 and 7-11 of paragraph bridging columns 1 and 2.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 1/27/06 have been fully considered but they are not persuasive. Applicant argues that the amendment requiring a non-covalent association between the polycation and the nucleic acid overcomes the rejection over Degols in view of Leonetti and Wiethoff because the cited art teaches a covalent linkage between the polycation and the nucleic acid. This is unpersuasive because the claims do not

exclude the presence of a covalent linkage, and Applicant has not shown that there is no ionic interaction in the composition of the cited art. Clearly if one would expect an ionic interaction to form between non-covalently linked polylysine and a nucleic acid in solution, then covalent linkage between polylysine and a nucleic acid only improves the likelihood of obtaining an ionic interaction. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

For these reasons the rejection is maintained.

Conclusion

Claim 8 is allowable. Claim 6 is objected to for depending from a rejected claim, but would be allowable if rewritten in independent form with all of the limitations of the claim from which it depends.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635